Ovarian cancers

Ovarian cancer is the second most common gynaecological malignancy and the major cause of death from gynaecological cancer in the UK. When detected in its early stages, ovarian cancer has an excellent prognosis.

Incidence

The lifetime risk of developing ovarian cancer in the general population is 1.4% (1 in 70), and the mean age of presentation is 64 years.. It is now increasingly accepted that a large proportion of ovarian cancers may in fact originate in the Fallopian tube, rather than the ovarian surface epithelium as previously thought.

Classification of ovarian cancer

1 Epithelial ovarian tumours (80%)	High-grade serous Endometrioid Clear cell Mucinous Low-grade serous (Borderline)
2 Sex cord stromal tumours (10%)	Granulosa cell Sertoli–Leydig Gynandroblastoma
3 Germ cell tumours (10%)	Dysgerminoma Endodermal sinus (yolk sac) Teratoma Choriocarcinoma
	Mixed
4 Metastatic (including Krukenberg tumours)	

Histological classification of malignant ovarian tumours

The ovary is also a common site for metastatic spread; Krukenberg tumours are ovarian metastases associated with primary cancers of the colon, stomach and breast.

Epithelial tumours

Epithelial tumours of the ovary can be benign, malignant or borderline.

Approximately 10% of epithelial tumours are classified as borderline ovarian tumours (BOTs).These tumours are well differentiated, with some features of malignancy (nuclear pleomorphism, cellular atypia) but do not invade the basement membrane. BOTs spread to other abdominopelvic structures (peritoneum, omentum) but do not often recur following initial surgery.

The majority of BOTs are serous tumours.

Mucinous BOTs may actually arise from appendiceal carcinomas of low malignant potential and can be associated with pseudomyxoma peritoneii. High-grade serous carcinomas account for around 75% of all epithelial ovarian cancers; mucinous and endometrioid tumours are less common, accounting for 10%, followed by clear cell carcinomas.

Highgrade serous tumours are characterized histologically by concentric rings of calcification, known as '**psammoma bodies'.**

Mucinous carcinomas are generally large multiloculated tumours associated with pseudomyxoma peritoneii.

Endometrioid carcinomas are similar in histological appearance to endometrial cancer, are associated with endometriosis in approximately 10% of cases and also a synchronous separate endometrial cancer in 10–15%.

They tend to be well differentiated and are associated with a better survival than high-grade serous carcinomas.

Clear cell carcinomas can also arise from endometriosis and are characterized histologically by clear cells, much like renal cancer.

Etiology and risk factors

Epithelial ovarian cancers include a heterogeneous group of tumours of different histological subtypes and aetiologies that affect the ovary, Fallopian tube and peritoneum.

High-grade pelvic serous carcinomas

Because most high-grade pelvic serous carcinomas present with advanced disease involving the ovary, Fallopian tube and peritoneal surfaces, it is often impossible to establish the anatomical site of origin. Assigning primary tumour site is of little clinical relevance anyway since the behavior, prognosis and treatment of these tumours are identical.

Endometrioid, mucinous, clear cell, borderline and low-grade serous ovarian carcinomas

Inclusion cysts of the ovarian surface epithelium and endometriosis give rise to neoplasms that are distinctly ovarian in origin, and can include mucinous, endometrioid, clear cell, borderline and low-grade serous carcinomas. Endometriosis-associated ovarian cancers are usually of endometrioid or clear cell histological subtype.

Risk factors in ovarian cancer

Decreased risk of ovarian cancer	Increased risk of ovarian cancer
Multiparity	Nulliparity
Combined oral contraceptive pill (RR reduced by up to 50%)	Intrauterine device (RR 1.76)
Tubal ligation	Endometriosis
Salpingectomy	Cigarette smoking (mucinous tumours only)
Hysterectomy	Obesity

Genetic factors in ovarian cancer

It is estimated that at least 10–15% of women with epithelial ovarian cancer have a hereditary predisposition. Women with mutations in BRCA1, BRCA2 and Lynch syndrome have an increased lifetime risk of epithelial ovarian cancer.

The lifetime risk in the general population is one in 70 (1.4%). This rises to 1 in 20 (5%) if women have one family member affected by a defect in one of these genes and further increases to 40–50% if two first-degree relatives are affected.

Hereditary cancers usually occur around 10 years before sporadic cancers and are associated with other cancers (particularly of the breast, colon and rectum). The most common hereditary cancer is the breast ovarian cancer syndrome (BRCA), accounting for 90% of the hereditary cancers. This syndrome is due to a mutation of tumour suppressor genes BRCA1 (80%) and BRCA2 (15%).

Lynch syndrome is hereditary non-polyposis colorectal cancer (HNPCC) and is associated with endometrial cancer and a 10% lifetime risk of ovarian cancer.

Preventing ovarian cancer

Women who test positive for a BRCA mutation are offered risk-reducing prophylactic BSO when they have completed their families.

This can usually be performed laparoscopically. Prophylactic surgery reduces the risk of ovarian cancer (by 90%) and premenopausal breast cancer (by 50%), although it does not eliminate the risk of primary peritoneal cancer.

Screening

Screening using transvaginal ultrasound scan (TVUSS) and CA125 measurement has not been shown to improve survival in women with a familial predisposition to ovarian cancer. This is because the highgrade serous tumours that are associated with BRCA mutation carrier status develop rapidly and most are at an advanced stage before they can be picked up by screening.

Clinical features

Most women with ovarian cancer have symptoms; however, these symptoms are **non-specific** and often **vague**. The difficulty with clinical diagnosis is the main reason that patients with ovarian cancer present with late stage disease (66% present with stage 3 disease or greater), and this has a dramatic effect on survival.

The most common symptoms are:
- Increased abdominal girth/bloating.
- Persistent pelvic and abdominal pain.
- Difficulty eating and feeling full quickly.

Other symptoms such as change in bowel habit, urinary symptoms, back ache, irregular bleeding and fatigue occur frequently and any women with persistence of these symptoms should be assessed .

The differential diagnosis of a pelvic mass includes non-epithelial ovarian cancer, tubo-ovarian abscess, endometriomas or fibroids.

Chest examination is important to assess for pleural fluid and the neck and groin should be examined for enlarged nodes.

Diagnosis and investigation

- **TVUSS :** is the initial imaging modality of choice to check for pelvic pathology

A pelvic mass is characterized in terms of its size, consistency, the presence of solid elements, bilaterality, the presence of ascites and extraovarian disease, including peritoneal thickening and omental deposits.

- **tumour markers** . CA125 is a non-specific tumour marker that is elevated in over 80% of epithelial ovarian cancers. It is only raised in approximately 50% of early-stage epithelial ovarian cancers and is also commonly raised in benign conditions such as pregnancy, endometriosis and alcoholic liver disease.

The Risk of Malignancy Index (RMI) is calculated from menopausal status, pelvic ultrasound features and CA125 level to triage pelvic masses into those at low, intermediate and high risk of malignancy.

- CT SCAN : Pelvic pathology at intermediate or high risk of malignancy is further imaged using computed tomography (CT) which is particularly useful for assessment of extrapelvic disease and for staging .

- MRI : magnetic resonance imaging scans.The MRI scan helps define tissue planes and operability.

Other investigations required for preoperative work-up include **chest X-ray,** electrocardiography **(ECG), full blood count, urea and electrolytes**, and **liver function tests.**

If the patient presents with gross ascites or pleural effusion**, paracentesis or pleural aspiration** may be required for symptom relief and/or diagnosis. A sample of the fluid removed is sent for **cytological assessment**.

If the diagnosis is uncertain or if primary chemotherapy is being considered (for advanced disease, or in patients not fit to undergo surgery), **a biopsy** is needed before treatment can be given. This is performed laparoscopically or radiologically **(ultrasound or CT-guided biopsy**). Usually the **omentum** is a good site for biopsy.

Tumour markers used in ovarian cancer diagnosis and follow-up

Tumour Marker	Tumour type	Uses
CA 125	Epithelial ovarian cancer, (Serous) borderline ovarian tumours	Preoperative, follow-up
CA 19-9	Epithelial ovarian cancer, (Mucinous) borderline ovarian tumours	Preoperative, follow-up
Inhibin	Granulosa cell tumours	Follow-up
hCG	Dysgerminoma, Choriocarcinoma	Preoperative, follow-up
AFP	Endodermal yolk sac, Teratoma	Preoperative, follow-up

AFP, α-fetoprotein; hCG, human chorionic gonadotrophin.

International Federation of Gynecology and Obstetrics (FIGO) staging of ovarian cancer

Stage	FIGO definition
1	Tumour confined to ovaries
1a	Limited to one ovary, no external tumour, capsule intact, no ascites
1b	Limited to both ovaries, no external tumour, capsule intact, no ascites
1c	Either 1a or 1b, but tumour on surface of ovary or with capsule ruptured or with ascites positive for tumour cells
2	Tumour confined to pelvis
2a	Extension and/or metastases to uterus or tubes
2b	Extension to other pelvic organs
2c	As 2a or 2b, but tumour on surface of ovary or with capsule ruptured or with ascites positive for tumour cells
3	Tumour confined to abdominal peritoneum or positive retroperitoneal or inguinal lymph nodes
3a	Tumour grossly limited to pelvis with negative nodes, but histologically confirmed microscopic peritoneal implants
3b	Abdominal implants <2 cm in diameter
3c	Abdominal implants >2 cm diameter or positive retroperitoneal or inguinal lymph nodes
4	Distant metastases. Must have positive cytology on pleural effusion, liver parenchyma

Management

Surgery

Provided the patient is fit to undergo anaesthesia, surgery remains necessary for diagnosis, staging and treatment of epithelial ovarian cancer. If the patient is at high risk of ovarian cancer, the surgery should only be performed by a gynaecological oncologist, as this has been shown to improve outcomes.

The objective of surgery is to stage accurately the disease and remove all visible tumour. This is vitally important in ovarian cancer as many studies indicate that the most important prognostic factor is no residual disease following laparotomy.

A vertical incision is required to gain access to all areas of the abdomen. Ascites or peritoneal washings are sampled and a total abdominal hysterectomy and BSO performed along with an omentectomy.

Occasionally, young patients who are found to have an early-stage epithelial ovarian cancer wish to have conservative, **fertilitysparing surgery**. In these cases, unilateral **salpingo–oophorectomy**, **omentectomy, peritoneal biopsies** and **pelvic/para-aortic node dissection** can be performed with **endometrial sampling** to exclude a synchronous tumour.

Fertility-sparing surgery may also be performed in patients with **borderline tumours** if fertility is an issue, otherwise pelvic clearance should be performed.

If a patient is unfit or unwilling to have surgery, or if preoperative assessment indicates that complete debulking is unlikely to be achievable, primary chemotherapy may be offered.

Chemotherapy

Chemotherapy can be given as primary treatment, as an adjunct following surgery or for relapse of disease. It can be used to prolong clinical remission and survival or for palliation

First-line treatment is usually a combination of a platinum compound with paclitaxel. Most regimes are given on an outpatient basis, 3 weeks apart for six cycles.

Following completion of chemotherapy, patients have a further CT scan to assess response to treatment. This scan can be used for comparison in the future if there is clinical or biochemical evidence of recurrence. Follow-up of patients includes clinical examination and CA125 measurement.

Prognosis

The survival figures depend on:
1- stage at presentation.
2- volume of disease following surgery .
3- the histological type and grade of tumour.
4- Age at presentation.

Primary peritoneal carcinoma

Primary peritoneal carcinoma (PPC) is a high-grade pelvic serous carcinoma. It is histologically indistinct from tumours arising from the Fallopian tube or ovary. There are, however, morphological differences between the two groups based on clinical findings at laparotomy.

Criteria for diagnosis includes:

- Normal sized or slightly bulky ovaries.
- More extraovarian disease than ovarian disease.
- Low volume peritoneal disease.

The clinical behaviour, prognosis and treatment is the same as for other high-grade pelvic serous carcinomas, although there is a trend towards using primary chemotherapy as complete surgical debulking is difficult.

Sex cord stromal tumours

These tumours account for approximately 10% per cent of ovarian tumours, but almost 90% cent of all functional (i.e. hormone-producing) tumours. Generally, they are tumours of low malignant potential with a good long-term prognosis.

Some morbidity may arise from the oestrogen (granulosa, theca or Sertoli cell) or androgen production (Seroli–Leydig or steroid cell) characteristic of these tumours, resulting in precocious puberty, abnormal menstrual bleeding and an increased risk of endometrial cancer.

The peak incidence is around the age of the menopause, although juvenile granulosa cell tumour usually presents in girls under 10 years of age, causing precocious puberty. Overall, granulosa cell tumours are the most common subtype, accounting for over 70% of sex cord stromal tumours.

Clinical features

A significant percentage of these tumours present with manifestations of their hormone production, typically irregular menstrual bleeding, postmenopausal bleeding or precocious puberty in young girls.

Granulosa cell tumours may present as a large pelvic mass or with pain due to torsion/haemorrhage. Sertoli–Leydig cell tumours produce androgens in over 50% of cases. Patients present with a pelvic mass and signs of virilization.

Common symptoms are amenorrhoea, deep voice and hirsutism. Occasionally, this group of tumours produce oestrogen and rarely renin, causing hypertension. Most sex cord stromal tumours present as unilateral ovarian masses, measuring up to 15 cm in diameter.

Macroscopically, the tumour is often solid with areas of haemorrhage, and the cut surface may be yellow due to high levels of steroid production. Granulosa cell tumours produce inhibin, which can be used for follow-up surveillance; levels often rise prior to clinical detection of recurrence.

Treatment

Treatment is based on the patient's age and wish to preserve fertility. If the patient is young, unilateral salpingo-oophorectomy, endometrial sampling and staging is sufficient.

In the older group, full surgical staging is recommended.

Granulosa cell tumours can recur many years after initial presentation and longterm follow-up is required. Recurrence is usually well defined and surgery is the mainstay of treatment as there is no effective chemotherapy regime.

Germ cell tumours

Malignant germ cell tumours occur mainly in young women and account for approximately 10% of ovarian tumours. They are derived from primordial germ cells within the ovary and because of this may contain any cell type.

The emphasis of management is based mainly on fertility-preserving surgery and chemotherapy.

The most common presenting symptom is a pelvic mass; 10% present acutely with torsion or haemorrhage and due to the age incidence, some present during pregnancy. Seventy per cent of germ cell tumours are stage 1; spread is by lymphatics or blood borne.

Dysgerminomas account for 50% of all germ cell tumours. They are bilateral in 20% of cases and occasionally secrete human chorionic gonadotrophin **(hCG).**

Endodermal sinus yolk sac tumours are the second most common germ cell tumours, accounting for 15% of the total. They are rarely bilateral and secrete α-fetoprotein **(AFP**).They present with a large solid mass that often causes acute symptoms with torsion or rupture. Spread of endodermal sinus tumours is a late event and is usually to the lungs.

Immature teratomas account for 15–20% of malignant germ cell tumours and about 1% of all teratomas. They are classified as mature or immature depending on the grading of neural tissue present. About one-third of teratomas secrete **AFP**.

Occasionally, there can be malignant transformation of a cell type within a mature teratoma. The most common cell type to transform is the epithelium, usually squamous cell carcinoma.

Non-gestational choriocarcinomas are very rare, usually presenting in young girls with irregular bleeding and very high levels of **hCG**.

Clinical features

Germ cell tumours should be suspected if a young woman presents with a large solid ovarian mass that is rapidly growing.

Tumour markers are measured preoperatively as this may influence the need for postoperative chemotherapy.

MRI is helpful to assess morphology, particularly within teratomas.
CT scaning of the abdomen allows assessment of the liver and lymph nodes.
A chest X-ray to exclude pulmonary metastases for all patients should have .

Treatment

most women presenting with malignant germ cell tumours are of reproductive age,so fertility-sparing treatment may be preferred.

An exploratory laparotomy is performed to remove the tumour and assess contralateral spread to the other ovary (20% in dysgerminoma). If there is a cyst present on the other ovary, this should be removed.

Careful inspection of the abdominal cavity is required with peritoneal biopsies and sampling of any enlarged pelvic or para-aortic nodes performed.

If metastatic disease is found, it should be debulked at surgery.
Intraoperative frozen sections may be required to assess nodal status.
Postoperative chemotherapy depends on stage of disease.